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10/078,927	02/19/2002	Thomas Curran	SJ-01-0032	6357

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/078,927	CURRAN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,10,11,13-15,32 and 35-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,10,11,13-15,32 and 35-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendices A, B*.

DETAILED ACTION

Status of the Application

[1] Claims 1, 4-8, 10-11, 13-15, 32, and 35-40 are pending in the application.

[2] Applicant's amendment to the claims, filed on 11/1/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's arguments filed on 11/1/07 in response to the Office action mailed on 8/6/07 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[5] The objection to the specification as introducing new matter by way of the specification amendments filed on 4/25/2005 and 11/21/2005 is maintained for the reasons of record and the reasons stated below. The objection was fully explained in a prior Office action. See particularly paragraph 6 beginning at p. 3 of the Office action mailed on 8/6/07.

RESPONSE TO ARGUMENT: Applicant argues (beginning at p. 7 of the instant response) the inclusion of a GenBank reference in the definition of "Dab1" is "more than a mere reference to material" and the examiner "agreed with this position when...the

Examiner previously determined that SEQ ID NOs:4 and 5 were intended to be incorporated by reference based on the inclusion of the appropriate genbank numbers". Applicant argues the examiner has previously determined that reference to a GenBank Accession, without an incorporation by reference statement, is considered to be an "inherent incorporation by reference" of a sequence and that this inclusion is not new matter.

Applicant's argument is not found persuasive. It is undisputed that there is no clear intent in the specification to incorporate by reference the sequences of GenBank Accession Numbers 3288851 and 1771281 by using the root words "incorporat(e)" and "reference". What appears to be in dispute is whether providing reference to GenBank Accession Numbers 3288851 and 1771281 in the specification at p. 4, lines 24-25 is sufficient to allow incorporation of the nucleotide sequences disclosed in GenBank Accession Numbers 3288851 and 1771281 into the specification by way of a sequence listing without adding new matter.

While the examiner may have previously taken the position that inclusion of SEQ ID NO:4 and 5 into the instant application does not add new matter, this was an erroneous position and, upon further consideration and in view of the proper standard for incorporation by reference, including the provisions set forth in 37 CFR 1.57 and MPEP 608.01(p), it is the examiner's current position, that the sequences of SEQ ID NO:4 and 5 of the sequence listing filed on 11/21/05 are new matter. See particularly paragraph 7 beginning at p. 2 of the Office action mailed on 5/1/06. Applicant continues to rely on the examiner's position prior to the 5/1/06 Office action as a basis for

traversing the instant rejection. However, it is noted that there would appear to be no prohibition against an examiner changing positions, particularly in view of the proper standard(s) to be applied in examination. According to MPEP 706, "An application should not be allowed, unless and until issues pertinent to patentability have been raised and resolved in the course of examination and prosecution, since otherwise the resultant patent would not justify the statutory presumption of validity (35 U.S.C. 282), nor would it "strictly adhere" to the requirements laid down by Congress in the 1952 Act as interpreted by the Supreme Court". As such, it would appear that the examiner's action was properly taken to raise and resolve "issues pertinent to patentability...in the course of examination and prosecution".

Applicant argues 37 CFR 1.57, which is used to support the objection, was added only on September 21, 2004, became effective on October 21,2004, and that MPEP 608.01(p) was not amended until October 21, 2004, where both occurrences were well after the instant application's filing date of February 19, 2002. Applicant further argues that even if held to the standard of 37 CFR 1.57, 37 CFR 1.57(g)(1) allows for correction to comply with 37 CFR 1.57(b)(1) if the application conveys an intent to incorporate the material by reference. According to applicant, because the specification discloses that the Dab1 proteins are defined as including proteins cloned from GenBank Accession numbers 328851 and 1771281, this is an indication of intent for these publications to be incorporated by reference.

Applicant's argument is not found persuasive. The examiner acknowledges citation of GenBank Accession Numbers 3288851 and 1771281 in the specification at p.

4, lines 24-25. However, according to MPEP § 608.01(p), incorporation by reference of material in a non-patent document "must be set forth in the specification and must: (1) Express a clear intent to incorporate by reference by using the root words "incorporat(e)" and "reference" (*e.g.*, "incorporate by reference"); and (2) Clearly identify the referenced patent, application, or publication." See 37 § 1.57(b). MPEP § 608.01(p) further states, "[i]f a reference to a document does not clearly indicate an intended incorporation by reference, examination will proceed as if no incorporation by reference statement has been made and the Office will not expend resources trying to determine if an incorporation by reference was intended."

It is noted that there is no clear intent to incorporate by reference the sequences of GenBank Accession Numbers 3288851 and 1771281 using the root words "incorporat(e)" and "reference" (*e.g.*, "incorporate by reference"), which is undisputed by applicant. Thus, according to MPEP § 608.01(p), "examination will proceed as if no incorporation by reference statement has been made." As such, the examiner considers the sequences of SEQ ID NO:4 and 5 to be new matter.

While applicant argues that 37 CFR 1.57 and MPEP 608.01(p) do not apply to this application by virtue of the application being filed prior to the effective date of 37 CFR 1.57 and the date of amendment of MPEP 608.01(p), the examiner can find no provision that excludes applications having a filing date of the instant application from being subject to 37 CFR 1.57 and MPEP 608.01(p) and applicant has presented no evidence of such. Thus, it is the examiner's position that the instant application is subject to the provisions of 37 CFR 1.57 and MPEP 608.01(p).

Further, it is noted that 37 CFR 1.57(g)(1) and (2) would not appear to apply in this case. 37 CFR 1.57(g)(1) states, "[a] correction to comply with paragraph (b)(1) of this section is permitted *only if the application as filed clearly conveys an intent to incorporate the material by reference*" (emphasis added). According to 37 CFR 1.57(b)(1), it appears that an application clearly conveys an intent to incorporate material "by using the root words 'incorporat(e)' and 'reference' (e.g., 'incorporate by reference')." As noted above and undisputed by applicant, the root words "incorporate" and "reference" do not appear to be used in association with the disclosed GenBank Accession Numbers. While the examiner acknowledges citation of GenBank Accession Numbers 3288851 and 1771281 in the specification at p. 4, lines 24-25, this appears to be "mere reference to material," which, according to 37 CFR 1.57(g)(1), "does not convey an intent to incorporate the material by reference."

Claim Objection

[6] Claim 11 is objected to in the recitation of "the polypeptide fragment TPAPRQSS(PO_4)PSKSSA (SEQ ID NO:3 which contains a phosphate group on the 8th amino acid)" and in order to improve claim form, it is suggested that the noted phrase be replaced with, for example, "SEQ ID NO:3".

[7] Claim 37 is objected to in the recitation of "QSSPSK (SEQ ID NO:1)" and "SSASHVSDPTADDIFEEGFESPSK (SEQ ID NO:2)" and in order to improve claim form, it is suggested that the noted phrases be replaced with, for example, "SEQ ID NO:1" and "SEQ ID NO:2", respectively.

Claim Rejections - 35 USC § 112, Second Paragraph

[8] The rejection of claims 36-40 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "candidate sequence preferred by cdk5 activity" is withdrawn in view of the instant claim amendment.

[9] The rejection of claim 39 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "GenBank accession number 1771281" is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 7 part b beginning at p. 7 of the Office action mailed on 8/6/07.

RESPONSE TO ARGUMENT: Applicant argues (beginning at p. 9, middle of the instant response) the intended nucleotide sequence encompassed by "GenBank accession number 1771281" is "limited to the sequence listed at the time of the invention...Applicants did not intend for claim 39 to encompass any polypeptides encoded by future revised sequences". According to applicant, since a skilled artisan "knows the filing date of the present application, that person can easily access the sequence in genbank that was known at that time".

Applicant's argument is not found persuasive. There appears to be no dispute that the sequences that are referenced by GenBank Accession Numbers are variable and can be revised over time. What appears to be in dispute is the scope of nucleic acids encompassed by the term "GenBank accession number 1771281". While

applicant argues this recitation is only intended to encompass the sequence of "GenBank accession number 1771281" that was available at the time of the invention, it is noted that there is no limitation in the claim or specific definition in the specification that limits the nucleotide sequence(s) referred to in the claim as "GenBank accession number 1771281" to that sequence or sequences disclosed by "GenBank accession number 1771281" at the time of the invention. Absent such a claim limitation or specification definition, the term "GenBank accession number 1771281" would appear to include any nucleic acid sequence that is encompassed by "GenBank accession number 1771281". As noted by MPEP 2111.01.I, "During examination, the claims must be interpreted as broadly as their terms reasonably allow".

It is known in the art that a GenBank Accession number does not change, regardless of whether the material disclosed by the Accession number changes, whereas the sequence disclosed by a Geneinfo Identifier does not. See Appendices A and B (material re-copied from NCBI Sample GenBank Record at ncbi.nlm.nih.gov/Sitemap/samplerecord, last viewed on 1/18/08). As such, while a skilled artisan would recognize that the sequence of a particular Geneinfo Identifier would not be variable, a skilled artisan would recognize that recitation of a GenBank Accession Number would not appear to exclude revisions to the material disclosed thereby. Thus, since the material encompassed by a GenBank Accession Number is variable, which is undisputed, it remains unclear as to the scope of nucleotide sequences that are encompassed by the recitation of "GenBank accession number 1771281".

[10] The rejection of claim 37 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "reference to amino acid positions of SEQ ID NO:1" and "reference to amino acid positions of SEQ ID NO:2" is withdrawn in view of the instant claim amendment.

Claim Rejections - 35 USC § 112, First Paragraph

[11] The new matter rejection of claims 1, 4-8, 10-11, 13-15, 32, and 35 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. See particularly paragraph 8 beginning at p. 9 of the Office action mailed on 8/6/07.

RESPONSE TO ARGUMENT: Applicant argues (beginning at p. 7 of the instant response) the inclusion of a GenBank reference in the definition of "Dab1" is "more than a mere reference to material" and the examiner "agreed with this position when...the Examiner previously determined that SEQ ID NOs:4 and 5 were intended to be incorporated by reference based on the inclusion of the appropriate genbank numbers". Applicant argues the examiner has previously determined that reference to a GenBank Accession, without an incorporation by reference statement, is considered to be an "inherent incorporation by reference" of a sequence and that this inclusion is not new matter.

Applicant's argument is not found persuasive. It is undisputed that there is no clear intent in the specification to incorporate by reference the sequences of GenBank

Accession Numbers 3288851 and 1771281 by using the root words "incorporat(e)" and "reference". What appears to be in dispute is whether reference to GenBank Accession Numbers 3288851 and 1771281 in the specification at p. 4, lines 24-25 is sufficient to provide adequate descriptive support for the sequences of SEQ ID NO:4 and 5 as recited in the claims.

While the examiner may have previously taken the position that inclusion of SEQ ID NO:4 and 5 into the instant application does not add new matter, this was an erroneous position and, upon further consideration and in view of the proper standard for incorporation by reference, including the provisions set forth in 37 CFR 1.57 and MPEP 608.01(p), it is the examiner's current position, that since the sequences of SEQ ID NO:4 and 5 of the sequence listing filed on 11/21/05 are new matter, recitation of SEQ ID NO:4 and 5 in the claims is also new matter. See particularly paragraph 9 beginning at p. 4 of the Office action mailed on 5/1/06. Applicant continues to rely on the examiner's position prior to the 5/1/06 Office action as a basis for traversing the instant rejection. However, it is noted that there would appear to be no prohibition against an examiner changing positions, particularly in view of the proper standard(s) to be applied in examination. According to MPEP 706, "An application should not be allowed, unless and until issues pertinent to patentability have been raised and resolved in the course of examination and prosecution, since otherwise the resultant patent would not justify the statutory presumption of validity (35 U.S.C. 282), nor would it "strictly adhere" to the requirements laid down by Congress in the 1952 Act as interpreted by the Supreme Court". As such, it would appear that the examiner's action was properly taken to raise

and resolve "issues pertinent to patentability...in the course of examination and prosecution".

Applicant argues 37 CFR 1.57, which is used to support the rejection, was added only on September 21, 2004, became effective on October 21,2004, and that MPEP 608.01(p) was not amended until October 21, 2004, where both occurrences were well after the instant application's filing date of February 19, 2002. Applicant further argues that even if held to the standard of 37 CFR 1.57, 37 CFR 1.57(g)(1) allows for correction to comply with 37 CFR 1.57(b)(1) if the application conveys an intent to incorporate the material by reference. According to applicant, because the specification discloses that the Dab1 proteins are defined as including proteins cloned from GenBank Accession numbers 328851 and 1771281, this is an intent for these publications to be incorporated by reference.

Applicant's argument is not found persuasive. The examiner acknowledges citation of GenBank Accession Numbers 3288851 and 1771281 in the specification at p. 4, lines 24-25 of the specification. However, according to MPEP § 608.01(p), incorporation by reference of material in a non-patent document "must be set forth in the specification and must: (1) Express a clear intent to incorporate by reference by using the root words "incorporat(e)" and "reference" (*e.g.*, "incorporate by reference"); and (2) Clearly identify the referenced patent, application, or publication." See 37 § 1.57(b). MPEP § 608.01(p) further states, "[i]f a reference to a document does not clearly indicate an intended incorporation by reference, examination will proceed as if no

incorporation by reference statement has been made and the Office will not expend resources trying to determine if an incorporation by reference was intended."

It is noted that there is no clear intent to incorporate by reference the sequences of GenBank Accession Numbers 3288851 and 1771281 using the root words "incorporat(e)" and "reference" (*e.g.*, "incorporate by reference"). Thus, according to MPEP § 608.01(p), "examination will proceed as if no incorporation by reference statement has been made." As such, upon reconsideration of the incorporation of the sequences of GenBank Accession Numbers 3288851 and 1771281 into the specification, the examiner considers the sequences of SEQ ID NO:4 and 5 to be new matter.

While applicant argues that 37 CFR 1.57 and MPEP 608.01(p) do not apply to this application by virtue of the application being filed prior to the effective date of 37 CFR 1.57 and the date of amendment of MPEP 608.01(p), the examiner can find no provision that excludes applications having a filing date of the instant application from being subject to 37 CFR 1.57 and MPEP 608.01(p) and applicant has presented no evidence of such.

Further, it is noted that 37 CFR 1.57(g)(1) and (2) would not appear to apply in this case. 37 CFR 1.57(g)(1) states, "[a] correction to comply with paragraph (b)(1) of this section is permitted *only if the application as filed clearly conveys an intent to incorporate the material by reference*" (emphasis added). According to 37 CFR 1.57(b)(1), it appears that an application clearly conveys an intent to incorporate material "by using the root words 'incorporat(e)' and 'reference' (e.g., 'incorporate by

reference')." As noted above and undisputed by applicant, the root words "incorporate" and "reference" do not appear to be used in association with the disclosed GenBank Accession Numbers. While the examiner acknowledges citation of GenBank Accession Numbers 3288851 and 1771281 in the specification at p. 4, lines 24-25, the is appears to be "mere reference to material," which, according to 37 CFR 1.57(g)(1), "does not convey an intent to incorporate the material by reference." As such, reference to the sequences of SEQ ID NO:4 and 5 in the claims is considered to be new matter.

[12] The new matter rejection of claim 40 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. See particularly paragraph 9 beginning at p. 12 of the Office action mailed on 8/6/07.

RESPONSE TO ARGUMENT: Applicant argues (beginning at p. 10, bottom of the instant response) SEQ ID NO:3 is a C-terminal fragment of Dab1 polypeptides from a variety of sources and is not present in proteins other than Dab1, even in closely related proteins. Applicant further argues the structural characteristic of SEQ ID NO:3 provides a distinguishing structural feature for the genus of recited Dab1 proteins and the use of this peptide as an antigen would indicate to a skilled artisan that this sequence is characteristic of Dab1 proteins and is useful for distinguishing Dab1 proteins from others. Applicant argues that the use of this peptide to generate antibodies to Dab1 would suggest to a skilled artisan that this peptide is a sequence that is characteristic of Dab1 and useful for distinguishing Dab1 from other polypeptides.

Applicant's argument is not found persuasive. There is no dispute that the amino acid sequence as shown in SEQ ID NO:3 may be present in other forms of a naturally occurring Dab1 protein or that the claim requires all members of the genus to have this common structural feature. What is at issue is whether or not the specification provides descriptive support for the method of claim 40. As acknowledged by applicant, the relevant portion of the specification to which applicant relies on as providing descriptive support for the Dab1 used in the method of claim 40, characterizes SEQ ID NO:3 as a phosphopeptide used as an antigen in the production of a phosphoantibody. According to the sequence listing filed on 11/21/05 and the specification at p. 6, lines 6-7, the sequence of SEQ ID NO:3 has a modification at amino acid position 8, wherein amino acid position 8 is a serine and the modification is phosphorylation. It is noted that based on the disclosure of the specification, this phosphorylated serine at position 8 corresponds to the serine whose phosphorylation state is indicative of Cdk5 activity and whose phosphorylation state is determined in the method of claim 40. Because SEQ ID NO:3 *requires serine at position 8 to be phosphorylated*, the Dab1 polypeptide comprising SEQ ID NO:3 as recited in claim 40 is *always* phosphorylated, *i.e.*, the Dab1 of claim 40 can never be in an unphosphorylated form. In this case, the specification would not appear to provide descriptive support for a Dab1 polypeptide that is always phosphorylated at position 491. Moreover, since the original application discloses methods for determining whether or not serine 491 is phosphorylated, one of skill in the art would recognize that the original application fails to provide descriptive support for a

method for determining whether or not serine 491 of a Dab1 is phosphorylated, wherein serine 491 of the Dab1 polypeptide is *always* phosphorylated.

[13] The written description rejection of claims 36-38 and 40 are rejected under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration of the rejection and in view of applicant's argument.

Under the heading of "Definitions", the specification defines "Dab1" as "an intracellular adapter protein that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity" (specification at p. 4, lines 22-23). According to MPEP 2111.01.IV, "An applicant is entitled to be his or her own lexicographer and may rebut the presumption that claim terms are to be given their ordinary and customary meaning by clearly setting forth a definition of the term that is different from its ordinary and customary meaning(s)...Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999)." As such, in view of the specification's express definition of "Dab1" as "an intracellular adapter protein that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity" (specification at p. 4, lines 22-23), this definition controls the meaning of a "Dab1" protein. According to applicant, "Rather than creating their own definition of Dab1...Applicants relied on the well known meaning of this term in the art and simply reiterated those features of Dab1 in the specification that are critical to its function in the claimed method". Indeed, there appears to be no indication

in the original application that the genus of "Dab1" proteins is meant to encompass polypeptides other than those that were known in the art at the time of the invention. Moreover, the novelty of the claimed invention does not appear to be in the Dab1 polypeptide itself, but, as applicant acknowledges, in the "discovery" of Dab1 phosphorylation by Cdk5.

[14] The scope of enablement rejection of claims 1, 4-8, 10-11, 13-15, 32, 35, and 37 under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration of the rejection and in view of applicant's argument, particularly with respect to the meaning of the term "Dab1" (see examiner's remarks immediately above) and discussion regarding Dab1 phosphorylation by Cdc2 at pp. 15-16 of the instant response.

[15] The scope of enablement rejection of claims 36, 38, and 40 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. See particularly paragraph 11 beginning at p. 20 of the Office action mailed on 8/6/07.

RESPONSE TO ARGUMENT: Applicant argues: 1) the examiner's cited evidence would not appear to conflict with determining Cdk5 activity by monitoring phosphorylation of amino acids 491 and/or 515 of Dab1; and 2) it was known in the art at the time of the invention how to make and screen for multiple modifications in Dab1 that allow Cdk5 phosphorylation and one of skill in the art can readily determine those Dab1 proteins that are useful for detecting Cdk5 activity.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification, while being enabling for a method for detecting Cdk5 serine kinase activity by determining whether serine at position 491 or 515 of Dab1 is or is not phosphorylated, wherein Dab1 phosphorylation at position 491 and/or 515 indicates Cdk5 serine kinase activity, does not reasonably provide enablement for the broad scope of claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Factors of *In re Wands* most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claim 36 is broadly drawn to a method for detecting Cdk5 activity by determining whether any serine of the carboxy terminal domain of Dab1 is phosphorylated. Claim 38 is broadly drawn to a method for detecting Cdk5 activity by detecting binding of a phosphoantibody generated against SEQ ID NO:3 to any serine of the carboxy terminal domain of Dab1. Claim 40 is broadly drawn to a method for detecting Cdk5 activity by determining whether any serine of the carboxy terminal domain of Dab1 comprising SEQ ID NO:3 is phosphorylated. According to the sequence listing filed on 11/21/05 and the specification at p. 6, lines 6-7, the sequence of SEQ ID NO:3 has a modification at amino acid position 8, wherein amino acid position 8 is a serine and the modification is phosphorylation. Because SEQ ID NO:3 requires serine at position 8 to be phosphorylated, the Dab1 polypeptide comprising SEQ ID NO:3 as recited in claim 40 is *always* phosphorylated, *i.e.,* the Dab1 of claim 40 can never be in an unphosphorylated form.

The methods encompass detection of Dab1 phosphorylation in both an unpurified biological sample, *e.g.,* brain and blood, and biological samples that have been clarified and purified.

The nature of the invention: According to applicant's remarks in the instant response at p. 12, bottom, the nature of the invention "is based on the discovery that Dab1 is specifically phosphorylated by Cdk5...a substrate which is selectively phosphorylated by Cdk5 had not heretofore been identified". See also the Appeal Brief filed on 1/18/07 at p. 7, which states, "The discovery that Dab1 is specifically phosphorylated on serine within a preferred candidate sequence by Cdk5 is the basis for the invention".

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: At the time of the invention, it was known in the art that Dab1 is phosphorylated on serine residues by Cdk5. For example, Homayouni et al. (*J. Neurosci.* 19:7507-7515, 1999; cited as reference AE2 in the IDS filed on 3/25/02) teaches "Dab1 contains a number of potential sites for serine kinases...and is phosphorylated by Cdk5 *in vitro*" (p. 7513, column 2, top). See also Curran et al. (US Patent 6,323,177), which teaches "In vitro cdk5 can also phosphorylate Dab1 on serine residues" (column 4, lines 46-47).

Also, at the time of the invention, methods for identifying a *potential* Cdk5 phosphorylation site based on the primary amino acid sequence of a polypeptide were known in the art. See, *e.g.,* the reference of Niethammer et al. (*Neuron* 28:697-711, 2000), which teaches that serine-proline in the amino acid sequence of a polypeptide

are potential Cdk5 phosphorylation sites in a polypeptide referred to as "NUDEL" (p. 698, Figure 1A) and an analysis of mouse and human Dab1 polypeptides (see GenBank Accession Numbers 1771281 and 3288851, respectively) reveals five such potential phosphorylation sites at serines 260, 400, 481, 491, and 515, which are followed by a proline.

However, the prior art fails to acknowledge which of those potential Cdk5 phosphorylation sites on Dab1 is truly indicative of and is specific for Cdk5 kinase activity. For example, Homayouni et al. teaches that Dab1 is serine phosphorylated in COS7 cells (p. 7511, Figure 5A-B), which lack endogenous Cdk5 kinase activity in the absence of a regulator protein. Homayouni et al. notes that Dab1 contains potential phosphorylation sites for casein kinase II and protein kinase C (p. 7513, column 2, top). See also Ohshima et al. (*Brain Res.* 1140:84-95, 2007; cited in the Office action 8/6/07), which teaches that Cdc2 is *at least* one other kinase that phosphorylates Dab1 on serine/threonine residues (*e.g.,* p. 85, right column, top and p. 86, Figure 1B) and as noted by Patrick et al. (*J. Biol. Chem.* 273:24057-24064, 1998; cited in the Office action mailed on 8/6/07), "[t]he substrate specificity of the p35/Cdk5 kinase is similar to that of the Cdc2 and Cdk2 kinases, phosphorylating the K(S/T)P*X*(K/R) consensus sequence motif" p. 24057, column 2, middle). As such, a skilled artisan would recognize the high level of unpredictability that a Dab1 polypeptide phosphorylated on any serine residue of the C-terminal domain as encompassed by the claims is necessarily indicative of Cdk5 serine kinase activity, particularly in a crude, unpurified biological sample as encompassed by the claims.

The amount of direction provided by the inventor and The existence of working examples: The specification discloses only two serine residues that are phosphorylated by Cdk5 and are thus indicative of Cdk5 activity, *i.e.,* serines 491 and 515 of mouse and human Dab1. Other than these residues, the specification fails to teach other residues of Dab1 that are phosphorylated by and are indicative of Cdk5 kinase activity. Moreover, it is noted that the specification fails to provide guidance as to how one is to detect Cdk5 activity by detecting phosphorylation at position 491 of a Dab1 polypeptide that is *always* phosphorylated at position 491 (as encompassed by claim 40).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of identifying potential phosphorylation sites within a protein were known in the art at the time of the invention, it was not routine at the time of the invention to identify which phosphorylation sites within a Dab1 are indicative of Cdk5 activity in a crude biological sample and which of those residues is phosphorylated, but not by Cdk5, particularly as the prior art acknowledges that serine/threonine kinases other than Cdk5 are known to phosphorylate Dab1.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of required experimentation, it is the examiner's position that undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims

must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

[16] The rejection of claims 1, 6-8, 15, 36-37, and 39-40 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Homayouni et al. (*J. Neurosci.* 19:7507-7515, 1999; cited as reference AE2 in the IDS filed on 3/25/02) as evidenced by Patrick et al. (*J. Biol. Chem.* 273:24057-24064, 1998; cited in the Office action mailed on 8/6/07) is withdrawn upon further consideration of the rejection and in view of applicant's argument noting that COS7 cells, while expressing Cdk5, would not appear to express *catalytically active* Cdk5 kinase, which requires the presence of a regulator protein (instant remarks at p. 19, middle), and the reference of Yamochi et al. (*Eur. J. Biochem.* 268:6076-6082, 2001), "In COS7 cells, cdk5 activity is...undetectable" (p. 6081, column 2, middle).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

> would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[17] Claim(s) 1, 6-8, 36-37, and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curran et al. (US Patent 6,323,177; "Curran") in view of Keshvara et al. (*J. Biol. Chem.* 276:16008-16014, 2001; "Keshvara"), Niethammer et al. (*Neuron* 28:697-711, 2000; "Niethammer"), and GenBank Accession Numbers 1771281 and 3288851.

The claims are drawn to methods of detecting Cdk5 serine kinase activity in a biological sample, by determining whether Dab1 is phosphorylated on a serine residue.

The reference of Curran teaches "In vitro cdk5 can also phosphorylate Dab1 on serine residues" (column 4, lines 46-47) and "In particular, identification of the site of Dab1 phosphorylation may permit its use as a potential target for agonists and antagonists. Cdk5 phosphorylates Dab1 in vitro. We can screen for inhibitors and agonists of this activity in connection with Reelin binding to VLDLR, and map the phosphorylation sites. Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD. Thus, this area of exploration has significant relevance" (column 23, line 63 to column 24, line 4). Curran does not teach those residues of Dab1 that are phosphorylated by Cdk5; does not teach Dab1 is phosphorylated in biological sample, *e.g.*, brain and blood, from a mouse or human; and does not teach methods of measuring Cdk5 activity by determining whether or not Dab1 is phosphorylated at these residues.

The references of Niethammer and Keshvara are cited as showing various methods for analysis of a phosphoprotein. Niethammer teaches a method for determining the sites of phosphorylation of a substrate polypeptide of Cdk5. For example, the method involves immunoprecipitation of the substrate polypeptide from mouse brain extracts with or without catalytically active Cdk5 activity and determining whether or not the substrate protein has altered electrophoretic mobility (p. 704, Figures 7A, 7D, and 7E and p. 709, column 1); teaches identifying those amino acids that are potentially phosphorylated by Cdk5 kinase in the primary sequence of the polypeptide, which have serine-proline (p. 703, column 2, bottom and p. 698, Figure 1A); individually and combinatorially mutating the potential Cdk5-phosphorylated serine or threonine residue to an alanine; and comparing the electrophoretic mobility shift in migration of immunoprecipitated wild-type and mutant proteins in the presence and absence of catalytically active Cdk5 in COS7 cells; and identifying those residues that are phosphorylated by Cdk5 by comparing the Cdk5 phosphorylation of the wild-type, individual mutants, and combinatorial mutants (p. 704, Figure 7F and p. 708, column 1 to p. 709, column 2).

The reference of Keshvara teaches a method of identifying sites of tyrosine phosphorylation of Dab1 by Src, using a method similar to that of Niethammer, wherein the tyrosine residues phosphorylated by Src are identified by mutating each potential Src-phosphorylated tyrosine to phenylalanine and analyzed by autoradiography and tryptic phosphopeptide analysis (p. 16009, Figure 1A-B and column 1 under *Kinase Reactions* and *Phosphopeptide Mapping;* p. 16010, Figure 2A-B). Keshvara teaches an

expression vector encoding Dab1 for use in expressing Dab1 in a eukaryotic cell (p. 16009, under *Cell Culture and Immunoprecipitations*).

GenBank Accession Numbers 1771281 and 3288851 disclose the amino acid sequences of murine Dab1 and human Dab1, respectively. Given these sequences at the time of the invention, a skilled artisan would have recognized that by visually inspecting the amino acid sequences of murine and human Dab1 as shown by GenBank Accession Numbers 1771281 and 3288851, respectively, five potential Cdk5 serine-proline phosphorylation sites (as noted by Niethammer) are present at positions 260, 400, 481, 491, and 515.

Therefore, at the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851 to immunoprecipitate Dab1 from mouse brain extract with and without catalytically active Cdk5 and analyze its electrophoretic mobility and to determine whether or not serine at position 260, 400, 481, 491, and 515 are phosphorylated by mutating Dab1 serines at positions 260, 400, 481, 491, and 515 to alanine, individually and combinatorially, and determining the serine(s) that is/are phosphorylated by Cdk5 in accordance with the methodology of Niethammer and Keshvara. By doing this, one of ordinary skill in the art would have practiced the active method step(s) as recited in the claims. One would have been motivated to do this because of the teachings of Curran that Cdk5 phosphorylates serines of Dab1 and the sites of Cdk5 phosphorylation of Dab1 can be identified and exploited to screen for agonists and antagonists as described above. One would have

had a reasonable expectation of success for mutating Dab1 serines at positions 260, 400, 481, 491, and 515 to alanine, individually and combinatorially, and determining the serine(s) that is/are phosphorylated by Cdk5 using the methodology of Niethammer and Keshvara because of the results of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851. Therefore, claims 1, 6-8, 36-37, and 39-40, drawn to methods for detecting Cdk5 activity would have been obvious to one of ordinary skill in the art at the time of the invention.

[18] Claim(s) 10-11, 13-15, 32, 35, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curran in view of Keshvara, Niethammer, and GenBank Accession Numbers 1771281 and 3288851 as applied to claims 1, 6-8, 36-37, and 39-40 above and further in view of Howell et al. (*Genes Develop.* 13:633-648, 1999; cited as reference AY1 in the IDS filed on 3/25/02; "Howell"), Fu et al. (*Nature Neurosci.* 4:374-381; "Fu"), Michalewski et al. (*Analytical Biochem.* 276:254-257, 1999; "Michalewski"), and Zhen et al. (*J. Neurosci.* 21:9160-9167, 2001; "Zhen").

The claims are drawn to methods of detecting Cdk5 serine kinase activity in a biological sample, by determining whether Dab1 is phosphorylated on a serine residue. The claims limit the method of detection of Dab1 phosphorylation to using an antibody that binds to Dab1 only when it is phosphorylated on serine or to an antibody generated against SEQ ID NO:3.

The references of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851 disclose the teachings as set forth above. The

combination of references does not appear to teach or suggest using a phosphoserine antibody, optionally against SEQ ID NO:3, in the methods disclosed therein.

As noted above, at the time of the invention, methods for analyzing protein phosphorylation were well known in the art. Particularly well-known were methods for analyzing phosphorylation of a polypeptide using antiphosphoamino acid antibodies. See particularly Michalewski, which teaches a polyclonal antiphosphoserine antibody (p. 254, column 2, middle) and Zhen, which teaches a monoclonal antiphosphoserine antibody (p. 9161, column 2, middle).

Howell teaches a method for analyzing *in vivo* and *in vitro* Dab1 tyrosine phosphorylation using an anti-tyrosine antibody (p. 645, Figures 2-3 and p. 646, Figure 4).

Fu teaches a method for analyzing Cdk5 serine phosphorylation of ErbB3 using an anti-phosphoserine antibody (p. 377, Figure 5; p. 379 under "*Chemicals and antibodies*; and p. 380 under In vitro *phosphorylation assay*).

Therefore, at the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Curran, Niethammer, Keshvara, GenBank Accession Numbers 1771281 and 3288851, Howell, Fu, Michalewski, and Zhen to analyze the phosphorylation of mouse or human Dab 1 at positions 260, 400, 481, 491, and 515 by using a monoclonal or polyclonal anti-phosphoserine antibody. While it is acknowledged that the prior art does not teach or suggest the use of an anti-phosphoserine antibody against SEQ ID NO:3 herein as recited in claims 11, 32, 35, and 38, it is noted that such an antibody is viewed as a "product-by-process"-type

limitation. According to MPEP 2113, "'[i]f the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe,* 777 F.2d 695,698,227 USPQ 964,966 (Fed. Cir. 1985)... Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi,* 710 F.2d 798,802,218 USPQ 289,292 (Fed. Cir. 1983). One would have been motivated to do this because Curran expressly teaches that Cdk5 phosphorylates serines of Dab1 and the sites of Cdk5 phosphorylation of Dab1 can be identified and exploited to screen for agonists and antagonists as described above and the use of an anti-phosphoserine antibody to detect phosphoserine avoids of the use of radioactivity. One would have had a reasonable expectation of success to analyze the phosphorylation of mouse or human Dab 1 at positions 260, 400, 481, 491, and 515 by using an anti-phosphoserine antibody because of the results of Curran, Niethammer, Keshvara, GenBank Accession Numbers 1771281 and 3288851, Howell, Fu, Michalewski, and Zhen. Therefore, claims 10-11, 13-15, 32, 35, and 38, drawn to methods for detecting Cdk5 activity would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[19] Status of the claims:

Claims 1, 4-8, 10-11, 13-15, 32, and 35-40 are pending.

Claims 1, 4-8, 10-11, 13-15, 32, and 35-40 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

APPENDIX A

ACCESSION

The unique identifier for a sequence record. An accession number applies to the complete record and is usually a combination of a letter(s) and numbers, such as a single letter followed by five digits (e.g., U12345) or two letters followed by six digits (e.g., AF123456). Some accessions might be longer, depending on the type of sequence record.

Accession numbers do not change, even if information in the record is changed at the author's request. Sometimes, however, an original accession number might become secondary to a newer accession number, if the authors make a new submission that combines previous sequences, or if for some reason a new submission supercedes an earlier record.

APPENDIX B

GI	"GenInfo Identifier" sequence identification number, in this case, for the protein translation. The **GI** system of sequence identifiers runs parallel to the **accession.version** system, which was implemented by GenBank, EMBL, and DDBJ in February 1999. Therefore, if the protein sequence changes in any way, it will receive a new GI number, and the suffix of the protein_id will be incremented by one.